UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/435,733	11/08/1999	ALPHONSE GALDES	CIBT-P02-052	5606

28120 7590 03/23/2004

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/435,733	GALDES ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,6,10,11,13-15,19-23,30,31,41,46 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2,6,10,11,13-15,19-23,30,31,41,46 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *July 14, 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 12/23/03, have been entered in full.

Response to Amendment

Withdrawn Rejections:

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office Action has been withdrawn in view of Applicant's amendments. Additionally, Applicant's argument on page 7, last paragraph, regarding the clarity of the term "the N-terminal amino acid residue" is persuasive

Maintained Rejections:

Claims 2, 6, 10, 11, 13, 14, 19, 20-23, 30, 31, 41, 46, 55 stand rejected under 35 U.S.C. 112, first paragraph, as set forth previously in item 7 of Paper 20, and recast in view of Applicant's amendments below. The specification, while being enabling for methods of treating and protecting against cisplatin and taxol induced neuropathy and a neuropathy resulting from sciatic nerve crush, or viral induced neuropathy comprising the systemic administration of sonic hedgehog polypeptide, wherein the polypeptide is modified at the either the C-terminal or N-terminal amino acid residue, does not reasonably provide enablement the treatment of any neuropathy comprising the systemic administration of a hedgehog agonist other than a polypeptide 100% identical to the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide, nor for internally modified hedgehog proteins. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

As discussed previously, Welty et al., *Soc. Neurosci. Abs.* 27(2)pp2621, 2001, report that systemic administration of sonic hedgehog did not alter the disease course in transgenic ALS mice. Further, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that systemic administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that, in the art of systemic administration of hedgehog for the treatment of peripheral neuropathies, only certain neuropathies are amenable to treatment (e.g. ALS is not) and of those that are (e.g. sciatic nerve crush), the specificity of the hedgehog agonist is critical, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not.

Additionally, while being enabling for the claimed methods comprising administering the N-terminal autoproteolytic fragment of sonic hedgehog wherein the protein is modified at the N-terminal amino acid residue, does not reasonably provide enablement for method comprising the administration of sonic hedgehog modified with a lipophilic moiety at an internal residue. specification provides no guidance as to which internal residues would be amenable to lipophilic modification. One skilled in the art would appreciate that lipid modification of an internal residue in the polypeptide completely changes the chemical identity of that residue. The specification provides only an invitation to perform random trial and error experimentation to identify which internal residues, if any, are amenable to change. Such extensive experimentation is unduly burdensome. Further, the art recognizes the difficulty in determining the effect of lipid

modification on an internal residue, e.g. WO 95/18856 (Ingham et al.) at page 34, and Jonassen et al. (e.g. page 2, lines 14-20), each teach that the lipophilic moiety be attached to either the N or C-terminal of the peptide. Nor, has the specification taught which fragments of sonic hedgehog would work as claimed. The specification has simply invited the artisan to begin an extensive research plan to randomly make and test fragments to try to find fragments that work as claimed. Such extensive experimentation is unduly burdensome.

Applicant argues that the claims have been amended to be consistent with the Examiner's recommendations. This argument has been fully considered but not deemed persuasive, for the several reasons detailed above.

Claims 2, 6, 10, 11, 13, 14, 19, 20-23, 30, 31, 41, 46, 55 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth previously and recast below in view of Applicants amendments.

The claims require *in vivo* methods of preventing dysfunction and/or degradation of functional performance of motor or sensory nerves comprising systemically administering a "therapeutic amount" or an "effect amount" of a fragment of a hedgehog polypeptide or a hedgehog protein that is encoded by a polynucleotide that hybridizes to a sonic hedgehog encoding polynucleotide. However one skilled in the art would not know which, if any, other than sonic hedgehog has the property of being efficacious for systemic administration in the treatment of peripheral neuropathies. There appears to be no description of such a particular

protein, nor guidance as to what structural characteristics such proteins must possess, nor are such known in the art. Nor has the specification put forth what structural characteristics a protein may have that allows it to function in the claimed method, yet also be structurally different than sonic hedgehog. As discussed above, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that systemic administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that, in the art of systemic administration of hedgehog in the treatment of peripheral neuropathies, the specificity of the hedgehog agonist is critical in some unknown way, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not. Applicant has not provided a guiding principle to allow one skilled in the art to know which hedgehog proteins, other than a naturally occurring sonic hedgehog protein and N-terminal autoproteolytically derived fragment thereof, are effective in treating any peripheral neuropathy.

Applicant argues that the claims have been amended to be consistent with the Examiner's recommendations. This argument has been fully considered but not deemed persuasive, for the several reasons detailed above.

Additionally, the claims have been amended to require a lipid modification that comprises addition of one or *more* lipophilic moieties to the N-terminal amino acid residue. There does not appear to be any mention of embodiments that encompass more than one lipophilic moieties to the N-terminal amino acid residue in the specification as filed, and nor would it be reasonably inferred by the skilled artisan that Applicant had contemplated such an

embodiment at the time of filing. Applicant is required to cancel this new matter in response to this office Action.

Reinstated Rejections:

Applicant's amendments have necessitated the reinstatement of the following rejections put forth in Paper 20, 2/7/02.

Claim Rejections - 35 USC § 102

Claims 2, 6, 10, 11, 13, 14, 15, 19, 20, 21, 23, 30, 31, 41, 46, 55 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/18856, Ingham et al., 13 July 1995.

Ingham et al., disclose that administration of sonic hedgehog can be used to treat conditions affecting the peripheral nervous system (pg 56, Line 27) e.g. viral or cisplatin induced neuropathy (pg 57, L24) or hereditary neuropathies such as amyotrophic lateral sclerosis (pg 56, L35), the severity of ALS being associated with age . Further, Ingham et al., disclose that the sonic hedgehog can be obtained from expression in mammalian or baculovirus expression systems (pg 111), both of which would necessarily result in a lipophilic modification of the protein with an aromatic, e.g. cholesterol modification and a fatty acid modification, e.g. palmitic acid (C_{16} alkyl). Further, the protein can be a fusion protein, e.g.c-myc (pg 112). Such treatments can be provided prophylactically (e.g. pge 57). Additionally, the sonic hedgehog protein used in the method taught be Ingham et al. would necessarily mimic hedgehog mediated signal transduction (e.g. claims 30 and 31), absent evidence to the contrary.

Claim Rejections - 35 USC § 103

Claims 2, 6, 10, 11, 13, 14, 15, 19, 20, 21, 30, 31, 41, 46, 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, as applied to claim 2, 6, 10, 11, 13, 14, 15, 19, 20, 21, 30, 31, 41, 46, 55 above, and in view of Porter JA *et al., Science* 274(255-259)1996. As set forth above, Ingham et al., disclose methods of treating peripheral neuropathies comprising the administration of sonic hedgehog polypeptides, however, Ingham et al., do not mention that the hedgehog polypeptide be modified with a lipophilic moiety. As set forth above, Ingham et al., disclose that the hedgehog polypeptides can be obtained from expression in mammalian or baculovirus expression systems (pg 111), both of which would necessarily result in a lipophilic modification of the protein with an aromatic, e.g. cholesterol modification and a fatty acid modification, e.g. palmitic acid (C_{12} alkyl).

Although the claims, in their current form, do not require that the sonic hedgehog polypeptides be isolated on the basis of a lipophilic moiety, the claims encompass such methods. Porter JA *et al.* disclose that mammalian hedgehog proteins derived from eukaryotic expression systems are conjugated to a cholesterol moiety, and suggest that this cholesterol modification is required for normal development in animals (see the Abstract). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to use cholesterol modified hedgehog protein as taught by Porter JA *et al.* when treating peripheral neuropathies as taught by Ingham et al. The motivation to do so was provided by Porter JA et al., who stated that the lack of cholesterol modification of hedgehog

may account for some of the undesirable effects of perturbed cholesterol biosynthesis on animal development (see the discussion).

Claims 2, 6, 10, 11, 13, 14, 15, 19, 20, 21, 23, 30, 31, 41, 46, 55 are rejected under U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, as applied to claim 2, 6, 10, 11, 13, 14, 15, 19, 20, 21, 23, 30, 31, 41, 46, 55 above, and in view of Pepinsky RB *et al.*, *J. Biol. Chem.* 273(22)14037-14045, 1996. As set forth above, Ingham et al., disclose methods of treating peripheral neuropathies comprising the administration of sonic hedgehog polypeptides, however, Ingham et al., do not mention that the hedgehog polypeptide be modified with a lipophilic moiety. As set forth above, Ingham et al., disclose that the hedgehog polypeptides can be obtained from expression in mammalian or baculovirus expression systems (pg 111), both of which would necessarily result in a lipophilic modification of the protein with an aromatic, e.g. cholesterol modification and a fatty acid modification, e.g. palmitic acid (C_{16} alkyl).

Although the claims, in their current form, do not require that the sonic hedgehog polypeptides be isolated on the basis of a lipophilic moiety, the claims encompass such methods. Pepinsky RB *et al.* disclose that sonic hedgehog expressed in eukaryotes is modified with a cholesterol moiety at the C-terminus and with a palmitic acid moiety at the N-terminus (see the Abstract). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to use palmitoyl modified hedgehog protein as taught by Pepinsky RB *et al.* when treating peripheral neuropathies as taught by Ingham et al. The motivation to do so was provided by Pepinsky RB *et al.* who stated

that palmitoylation of hedgehog increased the potency of hedgehog by about 30 percent (see the Abstract).

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, as applied to claim 2, 6, 10, 11, 13, 14, 15, 19, 20, 21, 23, 30, 31, 41, 46, 55 above, and in view off WO 96/29342, Jonassen et al., 26 Sep. 1996. As set forth above, Ingham et al., disclose methods of treating peripheral neuropathies comprising the administration of sonic hedgehog polypeptides, however, Ingham et al., do not mention that the hedgehog polypeptide be modified with a lipophilic moiety, e.g. derivatives such as phenanthrene, anthracene, naphthalene and naphthacene. Jonassen *et al.* teach the lipophilic moieties such as phenanthrene derivatives (e.g. page 4) are useful for modifying peptide hormones because such modifications protract the action of the peptides (see the Abstract for example). Further, Jonassen et al. teach that the particular derivative to use is a matter of routine optimization, depending on the particular disease to be treated (page 7). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to modify the sonic hedgehog peptide with phenanthrene or a derivative as suggested by Jonassen et al. when practicing the treatment methods of Ingham et al.. The motivation to do so was provided by Jonassen et al. who teach that lipophilic modification of peptide protracts the action of the modified peptides (see the Abstract).

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (571) 272-0871.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

March 19, 2004

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600